Targeting metabolic pathways to treat cardiovascular diseases

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Editorial

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Cardiovascular disease remains a leading cause of morbidity and mortality, and according to the World Health Organization represents an estimated 31% of all deaths worldwide. In the last two decades there is growing recognition of the importance of metabolism in the cardiovascular system as it was found that disturbances in cardiac metabolism often are at the basis of causing cardiac disease. As a biological pump, the heart's energy needs are enormous, being responsible for approximately 10% of whole-body fuel consumption [1]. However, apart from the critical role of energy metabolism, alterations in various metabolic pathways directly or indirectly impact on cardiac contractile function. These include post-translational protein modification, such as palmitoylation and O-GlcNAcylation, and metabolism-derived signals such as bioactive lipids. In line with the emergence of a pivotal role for energy metabolism, an increasing number of reports have indicated that interventions targeting metabolic pathways, referred to as 'metabolic modulation', are an effective approach to combat cardiovascular disease, in particular the most prevalent diseases of our time, *i.e.*, diabetes, heart failure, and the metabolic syndrome. Therefore, novel strategies and compounds directed at intermediary metabolism are being developed and already show high promise in the treatment of diabetes and heart failure. However, these strategies and/or compounds present numerous challenges concerning their actual mechanism and potential, requiring in-depth unraveling of their metabolic actions by the research community.

In order to foster interaction and collaboration among researchers in this specific field and provide an interactive learning environment for trainees, in 2001 the *Society for Heart and Vascular Metabolism* (SHVM) was founded at the initiative of William C. Stanley (who passed away untimely in 2013) [2]. Since 2003 the SHVM has held annual meetings which have become a "must" for any researcher working in the field of cardiac metabolism. Within the main topic of heart and vascular metabolism, each meeting is focused on a specific theme. These meetings have facilitated the establishment of many links and fruitful collaborations, which have led to a marked advance in our understanding of the role of cardiac energy metabolism in health and disease.

In 2015 it was decided that the results of the annual SHVM conferences should be made available to a wider audience. The editors of *Biochimica et Biophysica Acta* agreed to publish the proceedings of the 13th SHVM meeting, held in Tarrytown (New York, USA), in a Special Issue of BBA – Molecular Basis of Disease (BBA-DIS). In subsequent years the publishing of these proceedings in BBA-DIS has become a tradition. Table 1 lists the SHVM meetings held in 2015–2019 together with the bibliographic data of its proceedings. Thus, the 17th SHVM conference was held in Amsterdam, the Netherlands, on June 23–26, 2019, and focused on *Targeting metabolic pathways to treat cardiovascular diseases* (www.heartmetabolism.org/2019). As a result, the 5th Special Issue of BBA-DIS that is devoted to SHVM conference proceedings consists of 12 contributions from experts in the metabolic field who each review the state-of-the-art knowledge on a specific aspect of cardiac and vascular metabolism, thereby especially pinpointing promising areas for further research. Together, these review articles bring an overall picture of a further upheaval in metabolic-driven research and in therapeutic opportunities in our common battle against the most prevalent cardiovascular diseases.

The annual SHVM meeting started with a trainee workshop on human induced pluripotent stem (hiPS) cell-derived cardiomyocytes as a model system for research. Having been one of the pioneers in this specific field, Robert Passier presented an overview of the current status of the generation and application of hiPSC-cardiomyocytes [3]. While in recent years hiPSC-cardiomyocytes are more commonly being applied in research, they suffer from an immature phenotype which in many aspects resembles more that of the fetal heart than of the adult heart. Mechanical and electrical triggers for hiPSC cardiomyocyte maturation have been explored extensively, but only recently focus has shifted to improve maturation through metabolic parameters. In his contribution, metabolic changes occurring during human embryonic/postnatal development and maturation *in vivo* are taken as a blueprint for hiPSC-cardiomyocyte maturation *in vitro*. This approach includes, for instance, the addition of fatty acids to the culture medium so as to enhance maturation.

Subsequently, Paul Wijnker demonstrated how engineered heart tissue can be applied successfully to delineate specific pathology and treatment responses in patients with hypertrophic cardiomyopathy (HCM) [4]. HCM is the most common inherited cardiomyopathy but, with over 1500 associated mutations, many of which cause specific cellular perturbations. As a result, depending on the mutation, individual patients will need tailored treatment. Working with engineered heart tissue allows the evaluation of effective treatment options.

Targeting cardiac fatty acid metabolism is regarded as a primary approach for metabolic modulation therapy because of the importance of long-chain fatty acids as the main fuel for myocardial energy provision which requires a properly controlled rate of fatty acid utilization, avoiding both too low uptake rates, which could elicit an energy deficit, and too high uptake rates, which pose the risk of excess lipid accumulation and lipotoxicity. The latter is a main cause of cardiac insulin resistance and diabetic cardiomyopathy. In their contribution, Sander Houten and colleagues discuss the essential role of carnitine and carnitine acyl-transferases in not only mitochondrial fatty acid β-oxidation but also peroxisomal β-oxidation [5]. Specifically, the review discusses the physiological function of exchange of acylcarnitines between peroxisomes and mitochondria, an underexplored aspect that may serve a significant function in the proper handling by the heart of exogenous long-chain and medium-chain fatty acid species.

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Table 1
Overview of Special Issues devoted to heart and vascular metabolism (SHVM conferences).

Meeting	Year	City & organizers	Topic	Editorial
SHVM-13	2015	Tarrytown, NY, USA (R. Ramasamy, P.C. Schulze, I. Goldberg, A.M. Schmidt)	The role of post-translational protein modifications on heart and vascular metabolism	BBADIS 1862 (2016) 2197–2198
SHVM-14	2016	Beijing, China (R.-P. Xiao, E.D. Abel, X.-W. Chen)	Cardiac adaptations to obesity, diabetes and insulin resistance	BBADIS 1864 (2018) 1905–1907
SHVM-15	2017	Weimar, Germany (T. Doenst, M. Schwarzer)	The power of metabolism – Linking energy supply and demand with cardiac contractile function	BBADIS 1865 (2019) 725–727
SHVM-16	2018	Charleston, SC, USA (L.A. Cowart, M.E. Young)	Using unbiased discovery approaches for identifying novel mechanisms modulating cardiovascular metabolism	BBADIS 1866 (2020) xxx-xxx
SHVM-17	2019	Amsterdam, The Netherlands (J.F.C. Glatz, C.J. Zuurbier)	Targeting metabolic pathways to treat cardiovascular diseases	BBADIS 1866 (2020) xxx-xxx

The transmembrane glycoprotein CD36 (SR-B2) is the main myocardial fatty acid transporter and serves a pivotal role in the regulation of cellular fatty acid uptake. The rate of fatty acid uptake is dependent on the presence of CD36 in the sarcolemma, which is regulated by subcellular vesicular recycling of CD36 between endosomes and the sarcolemma. This mechanism has many similarities with the mechanism by which myocardial glucose uptake is regulated by the subcellular recycling of glucose transporter GLUT4. Together, CD36 and GLUT4 determine the substrate preference of the heart, *i.e.*, the fatty acid–glucose fuel balance. Recent studies by Joost Luiken et al. [6] have disclosed trafficking proteins that are distinctly involved in CD36 and GLUT4 vesicular trafficking. These trafficking proteins, in particular vacuolar-type H^+-ATPase and specific vesicle-associated membrane proteins (VAMPs), offer promising targets to rectify aberrant substrate uptake rates and restore a proper fatty acid–glucose fuel balance.

Following the exciting observation that treating diabetic patients with sodium-glucose co-transporter-2 (SGLT2) inhibitors (collectively known as gliflozins) has a marked beneficial effect on cardiovascular disease, reducing mortality and hospitalization for heart failure, the underlying mechanism has been hotly debated. Several studies have now revealed that part of the underlying beneficial mechanisms of the SGLT2 inhibitors can be ascribed to metabolism and ion homeostasis of the heart, not only providing a direction for therapy for diabetic and heart failure patients, but also implicating cardiac metabolism and ionic homeostasis as crucial underlying causal mechanisms of action of these most prominent novel diabetic (and presumably heart failure) medicines.

Julian Mustroph et al. [7] address the possible role of Ca^{2+}/calmodulin-dependent kinase II (CaMKII) and of GLUT1 in the cardiac beneficial effects of SGLT2i's. CaMKII is often upregulated and hyperactive in heart failure patients, and its hyperactivity is believed to contribute to the development of heart failure. In addition, the failing heart is believed to have a shortage of oxidizable substrates. Several studies have suggested that SGLT2i's can alter and improve cardiac metabolism. Recent work by his research group has delineated that empagliflozin, one of the most promising SGLT2i's for cardiac diseases, can directly attenuate CaMKII activity and increase GLUT1-associated glucose uptake into cardiomyocytes. The review discusses these findings and puts them in a broader perspective of the workings of SGLT2i's in relation to heart failure.

CaMKII and cardiac metabolism as possible cardiac beneficial mechanisms of empagliflozin were further evaluated in an experimental study by Michael Lehrke et al. [8]. They employed an animal model of type 2 diabetes (*db/db* mice on a high fat diet) treated with empagliflozin for 4½ weeks, and examined cardiac function and plasma metabolic substrate concentrations. The major findings of the study supported the cardiac beneficial effects of SGLT2 inhibitors: treatment with empagliflozin improved cardiac diastolic function, reduced mortality, improved glucose metabolism but was without effects in cardiac ketone and branched-chain amino acid metabolism.

The severity of post-myocardial infarction (MI) heart failure is to a large extent determined by the size of the initial infarct during the evolving MI and its clinical reperfusion treatment. Infarct size is not only a result of injury occurring during ischemia, but also during the initial period of reperfusion (so-called “reperfusion injury”), thereby offering therapeutic potential for interventions during reperfusion in order to reduce infarct size and, consequently, the degree of heart failure. Although SGLT2i's do not significantly affect the incidence of MI, recent pre-clinical studies show that these compounds may reduce reperfusion injury, infarct size and thus heart failure. This exciting novel hypothesis about the working of the SGLT2i's is further explored and discussed in the review by Ionanna Andreadou and co-authors [9], who concludes that the mitigation of reperfusion injury by SGLT2i's may be explained by its direct modulation of Na^+, Ca^{2+}, the sodium/hydrogen exchanger (NHE), CaMKII, STAT3, AMPK, inflammation and oxidative stress.

Epidemiological studies have clearly indicated that sex and gender affect the occurrence, development and consequences of cardiovascular diseases. For instance, the prevalence of cardiovascular disease is lower in non-menopausal women than in men of the same age, but it increases with age and in post-menopausal women becomes the major cause of mortality. Importantly, gender differences include biological but also socio-cultural parameters. The putatively complex molecular mechanisms underlying sex and gender differences in cardiac pathophysiology are still poorly understood. Renée Ventura-Clapier and co-workers review current knowledge on gender related differences in energy metabolism [10] to conclude that there is a lack of experimental and clinical studies addressing this issue. Furthermore, she argues that with experimental studies more care should be taken to consider and discuss gender issues and, at least, properly describe the gender studied (details that are lacking in many published experimental animal studies). Obviously, understanding gender issues is a prerequisite for developing personalized therapeutic strategies.

Loss of insulin action or function during obesity and diabetes is known to disrupt energy metabolism in the heart by triggering hyperglycemia and fatty acid over-utilization, leading to glucolipotoxicity. Thomas Pulinilkunnil and his team at Dalhousie University [11] have previously demonstrated that glucolipotoxicity negatively regulates the lysosomal protein degradation pathway or autophagy by inhibiting transcription factor EB (TFEB), a master regulator of lysosomal biogenesis and lysosomal function. In the current paper, they examine nutrient specific and upstream regulators of TFEB in the heart, as well as metabolic alterations in response to the loss of TFEB action, and explore whether these alterations impact on cardiomyocyte function. By utilizing *in vitro*, *ex vivo* and *in vivo* models of lipid overload, they demonstrate that saturated fatty acids (such as palmitate), in contrast to polyunsaturated fatty acids, decreases TFEB content in a concentration dependent manner. Thus, hearts from mice on high-fat/high-sucrose diet exhibited a decline in nuclear TFEB content, whereas adenoviral expression of constitutively active TFEB rescued glucolipotoxicity-induced lysosomal dysfunction and cell death. Together, their data indicate that loss of TFEB is sufficient to remodel substrate metabolism and to render the cardiomyocyte prematurely susceptible to nutrient overload-induced cell death.

Besides fatty acids and glucose, the heart may also use other substrates for energy provision, such as lactate, ketone bodies and amino acids [1]. In the last decade ketone bodies have emerged in particular focus because of several reports indicating their beneficial action on the failing heart. Ketone bodies serve in carbohydrate-depleted conditions as glucose-sparing energy substrates, but also have important signaling functions. Kieran Clarke and her group [12] has applied manipulation of ketone body metabolism to treat cardiac disease, especially by administering exogenous ketone esters, and in their review discuss the state-of-the-art on both our molecular understanding of the beneficial role of ketones for heart disease and practical aspects of its therapeutic application.

Structural and functional alterations in mitochondria have long been known to play a key role in the pathogenesis of ischemia-reperfusion (IR) injury in the heart. The mechanisms involved, such as induction of mitochondrial permeability transition or oxidative damage of intramitochondrial structures and molecules, are modulated or aggravated by mitochondrial ROS production, placing mitochondrial ROS at the center stage of IR injury. The general view is that mitochondrial oxidative stress is quite moderate during ischemia itself, but much more pronounced during the burst of ROS at the onset of reperfusion as well as during the hours and days following an ischemic insult. Moreover, novel sources of mitochondrial ROS beyond that directly related to the electron transport chain have been revealed, such as monoamine oxidases, the p66Shc protein, and NADPH oxidase 4. The comprehensive review by Heiko Bugger and Katharina Pfeil [13] provides an in-depth report on the various sources of mitochondrial ROS as well as the consequences of ROS, both in IR and post-infarction remodeling. The authors also point to the challenge of finding an effective treatment approach in human cardiac IR injury, which calls for additional studies and testing of new compounds or treatment strategies.

Finally, Edoardo Bertero, Christoph Maack and coworkers [14] discuss the essential role of cardiolipin in mitochondrial morphology, metabolism, and respiration. Mitochondrial membranes are characterized by a unique lipid composition, and are the only cellular membranes containing the phospholipid cardiolipin which play an essential role in mitochondrial morphology, metabolism, and respiration. Mitochondrial dysfunction has been implicated in the pathogenesis of numerous disorders. In this review the authors discuss cardiolipin biogenesis and function under physiological conditions and inherited disorders characterized by perturbed cardiolipin biosynthesis and remodeling, namely Barth syndrome (BTHS), dilated cardiomyopathy with ataxia (DCMA), and Sengers syndrome.

Taken together, the various reviews collected in this Special Issue of *Biochimica et Biophysica Acta – Molecular Mechanisms of Disease* present an updated understanding of the significance of metabolic homeostasis in the cardiovascular system. Myocardial energy metabolism remains a highly dynamic process that is pivotal for securing an optimal contractile function. Detailed insight into the underlying molecular mechanisms is essential for identifying additional diagnostic and therapeutic options to treat aberrations in cardiac functioning seen in the failing heart.

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Jan F.C. Glatz is Professor of Cardiac Metabolism at the faculty of Health, Medicine and Life Sciences (FHML) of Maastricht University, the Netherlands. Currently he serves as chair of the Department of Genetics & Cell Biology as well as deputy-chair of the Department of Clinical Genetics (Maastricht University Medical Center+). In the period 2012–2015 Dr. Glatz was President of the *Society for Heart and Vascular Metabolism* (SHVM). Dr. Glatz's major contributions to understanding cardiac metabolism include the disclosure of the molecular mechanism of cardiac fatty acid uptake, especially the role of membrane substrate transporters (in particular CD36/SR-B2) and that of cytoplasmic heart-type fatty acid-binding protein (FABP3), and the unraveling of the significance of altered cardiac fatty acid handling in obesity-induced cardiac insulin resistance and diabetic cardiomyopathy. He also put forward the apparent necessity for a fatty acid–glucose fuel balance for the heart to maintain its proper contractile function, and suggested that re-balancing cellular energy substrate metabolism is a promising approach to mend the failing heart. His main current scientific interests are (i) the regulation of energy metabolism (in particular substrate preference) in the healthy and diseased heart with focus on the application of intracellular membrane substrate transporter recycling for so-called metabolic modulation therapy, and (ii) the application of human iPS cell-derived cardiomyocytes for the functional characterization of genetic variants of unknown significance.

Coert J. Zuurbier is Associate Professor at the department of Anesthesiology, Amsterdam UMC, University of Amsterdam, The Netherlands. His long term research goals are (1) to elucidate molecular and physiological mechanisms of cell death and vascular damage in the heart, that contribute to the pathology of heart failure, stress hyperglycemia, diabetes and ischemia-reperfusion (I/R) injury, and (2) to develop clinical relevant strategies to combat cardiac cell death and vascular damage in the setting of stress hyperglycemia, heart failure, diabetes and acute ischemia/reperfusion. The focus is on deciphering and manipulation of the crucial cellular mechanisms underlying death/survival programs of the cardiac cell, in both acute (ischemia/reperfusion) and chronic (heart failure, diabetes) pathologies. The most important pioneering, reproducible, discoveries from his lab are (1) glycocalyx role in diabetes and hyperglycemia, (2) mitochondria-hexokinase binding role in cardiac infarction, metabolism, diabetes and cardioprotection, (3) interaction between anesthesia and metabolism, and (4) elucidation of cardiovascular mechanisms behind the kidney-targeted diabetes-heart failure novel drug class of SGLT2 inhibitors.

Terje S. Larsen is Professor in Physiology at the department of Medical Biology, Health Sciences Faculty of the Arctic University of Norway. For a number of years (1998–2005 and 2009–2017) he served as chair of the department of Medical Biology, and today he is leading the Cardiovascular Research Group, which is one of the research groups at the department. Since 2018, he has served as President of the Society for Heart and Vascular Metabolism (SHVM). Dr. Larsen and his collaborators have focused on alterations in myocardial metabolism during obesity and type 2 diabetes, and how such changes lead to cardiomyopathy and reduced cardiac efficiency (the relationship between cardiac work and oxygen consumption). The experimental activity includes use of various (lipid-lowering) PPAR agonists, exercise training, and dietary interventions to determine their impact on substrate utilization and mechanical function of the heart. Most recently, they have shown that dietary supplementation with small amounts of a novel marine oil reduces abdominal obesity, suppresses low-grade inflammation in adipose tissue, and improves insulin sensitivity in diet-induced obesity. This oil also has cardioprotective effects, in the sense that it improves the recovery of cardiac function following ischemia. Dr. Larsen currently is leading investigations to understand the mechanism(s) by which the oil may afford protection of the heart.

Jan F.C. Glatz[a,*], Coert J. Zuurbier[b], Terje S. Larsen[c]
[a] *Maastricht University, Maastricht, the Netherlands*
[b] *Amsterdam University Medical Center, Amsterdam, the Netherlands*
[c] *The Arctic University of Norway, Tromsø, Norway*
E-mail addresses: glatz@maastrichtuniversity.nl (J.F.C. Glatz), c.j.zuurbier@amsterdamumc.nl (C.J. Zuurbier), terje.larsen@uit.no (T.S. Larsen).

* Corresponding author.